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Letter to the Editors

Psychiatric adverse drug reactions to glucocorticoids in children and adolescents: a much higher risk with elevated doses

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Psychiatric and behavioural adverse drug reactions (ADRs) to glucocorticoids, especially when used at high dose, are multiple, unforeseeable and extend to a large spectrum of psychopathological disturbances [1–4]. Such high-dose glucocorticoids are frequently prescribed for children with chronic diseases such as asthma, nephrotic syndrome or following organ transplantation.

The present study to evaluate the occurrence of psychiatric and/or behavioural ADRs in children was performed using data obtained from the French Pharmacovigilance Database (FPD) to identify spontaneous reports containing such ADRs induced by glucocorticoids in children and adolescents (age < 18 years).

The French Pharmacovigilance System was first established in 1973 and consists of a network of 31 Regional Centres. The FPD was established in 1985 to record spontaneous reporting of ADRs. Furthermore, reporting 'serious' or 'unlabelled' ADRs to the French Regional Centres has been mandatory for any drug prescriber, physician, dentist or midwife in France since 1995 [5]. Despite this obligation, the reporting rate of ADRs in France remains very low. It is estimated at about 5–10% for 'serious' ADRs [6].

Spontaneous reports submitted to the FPD, in which glucocorticoids were suspected for psychiatric and/or behavioural ADRs in patients <18 years old, were extracted from 1 January 1985 to 30 March 2007. All spontaneous reports were reviewed and information concerning age, gender, different types of psychiatric ADRs, types of suspected glucocorticoid, dose and route of administration, indication, duration of treatment, time to onset, seriousness and evolution of ADRs was analysed.

Among the 455 spontaneous reports containing psychiatric and/or behavioural ADRs reported with glucocorticoids in the FPD from 1 January 1985 to 30 March 2007 (in both adults and children), 95 (20.9%) occurred in patients <18 years old, including 136 ADRs (Table 1). Fifteen cases were classified as 'serious' (one death and 14 hospitalizations). Mean age of the patients was 5.9 years and 57 were <6 years old. Glucocorticoid dose was unknown in 16 cases. ADRs occurred in 29 cases (30.5%) after prescription or administration errors [overdose ($n = 16$) or high dose ($n = 13$)]. They were observed in 13 other children (13.7%) after use of high ($n = 8$) or supratherapeutic ($n = 5$) doses for different therapeutic indications (i.e. serious asthma, nephrotic syndrome or leukaemia) (Figure 1). In four cases the indications were out of the recommendations of Summary Product Characteristics. So, off-label prescription or administration was present in 25 (26.3%) cases (21 overdose and four off-label indications). The most frequent ADRs were agitation or excitation and sleep disturbances. ADRs occurred most often by oral forms ($n = 72$), but were also reported after administration of intravenous or inhaled forms. In 75% of cases, the time to onset was <7 days. The majority of the ADRs (82 cases, 86.3%) recovered completely after glucocorticoid withdrawal. Glucocorticoids more frequently involved were betamethasone (38 cases), prednisolone (21 cases) and prednisone (17 cases).

Our data show that psychiatric and/or behavioural ADRs of glucocorticoids could also occur in children and adolescents and are frequently due to glucocorticoid overdose (22.1%) or high dosage (22.1%). The level of off-label prescription or administration associated with these ADRs is 26.3% (25 cases), which could be considered relatively high. However, the present results should be interpreted with caution because of the low reporting rate of ADRs in France [6]. Our study has also shown that the ADRs appear most often in the first week of glucocorticoid introduction. The main psychological ADRs are agitation and sleep

Table 1

Characteristics of psychological and/or behavioural ADR cases related to glucocorticoids, recorded in FPD, in patients <18 years old, from 1 January 1985 to 30 March 2007

Characteristics	Values
Spontaneous reports, *n*	95
'Serious' cases, *n* (%)	15 (15.9)
ADRs, *n* (%)	136 (100)
Agitation or excitation	59 (43.4)
Sleep disturbances	25 (18.4)
Psychotic symptoms	11 (8.1)
Maniac symptoms	11 (8.1)
Mental disorders	9 (6.6)
Food behaviour disorders	8 (5.9)
Confusional symptoms	8 (5.9)
Age, years	5.9 ± 5.1
Gender (male), *n* (%)	46 (48.4)
Patients ≤6 years old, *n* (%)	57 (60.0)
Prescription or administration errors, *n* (%)	29 (30.5)
Overdose	16 (16.8)
High dose	13 (13.7)
Therapeutic indications with high dose, *n* (%)	13 (13.7)
Supratherapeutic dose	5 (5.3)
High dose	8 (8.4)
Administration route, *n* (%)	
Oral	72 (69.9)
Intravenous	13 (12.6)
Inhaled	10 (11.7)

ADR, adverse drug reaction; FPD, French Pharmacovigilance Database.

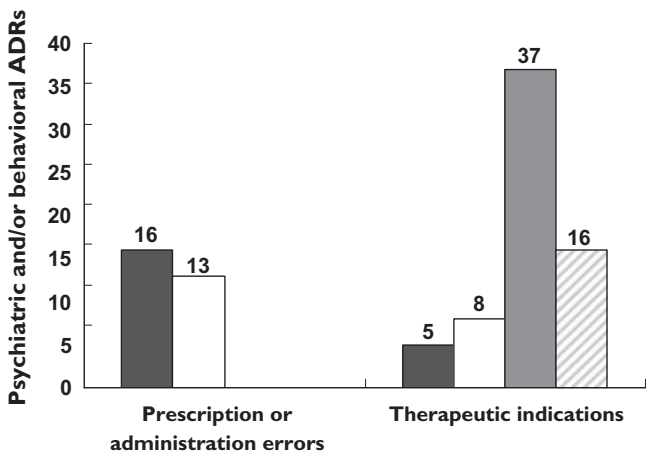

Figure 1

Psychiatric and/or behavioural adverse drug reactions (ADRs) recorded in the French Pharmacovigilance Database from 1985 to March 2007 according to the dose of glucocorticoids. Overdose, (■); High dose, (□); Normal dose, (■); Unknown dose, (◩)

disturbances. It appears to be necessary to inform health professionals about such ADRs, which are difficult to recognize because of their complex and heterogeneous clinical symptoms.

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